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Appendix A

Relationship between New Claim 204 and Claim 3 of the Krieg '646 Patent

"Method of treating an allergy in a vertebrate".

This is the preamble of Applicants' claim 204. Krieg claim 3 recites that the claimed method is for "desensitizing a subject against the occurrence of an allergic reaction in response to contact with a particular allergen". This in effect states that the method is directed to treatment of an allergy, which is recited in Applicants' claim 204. As is well known in the art, allergy treatment when using an antigen which causes the allergy, or an allergen,³ involves administering the offending antigen in an effort to "desensitize" the subject or vertebrate so that reaction to subsequent exposure to (or contact with) the offending antigen is reduced ("against the occurrence of an allergic reaction in response to contact with a particular allergen"; claim 3 of the Krieg '646 patent). Applicants' specification refers to "conventional immunotherapy protocols" and desensitization obtained by administering protein antigen. Page 36, lines 1-4 and lines 10-13; *see also* Example VI. Example VII shows a reduction of antigen-specific, allergen-associated IgE production in mice receiving an antigen-encoding plasmid that also contains an immunostimulatory, CG-containing sequence.

Krieg's '646 patent specification refers to using immunostimulatory nucleic acid molecules in "desensitization *therapy* for allergies" and that "the instant claimed nucleic acid molecules can be administered in conjunction with a particular allergen to a subject as a type of desensitization *therapy* to *treat* or prevent the occurrence of an allergic reaction." Col. 34, lines 6-9; col. 6, lines 62-65 (emphasis added). The Krieg '646 patent specification also makes the connection between the observed shift toward a Th1 response effected by the CG-containing immunostimulatory nucleic acids and the allergy context:

³ This is in contrast to other allergy "treatments" which do not involve administration of the offending antigen, and are thus not based on immunotherapy. Examples of these other types of "treatments" include antihistamines.

“Based on the ability of the immunostimulatory nucleic acid molecules to shift the immune response in a subject from a Th2 (which is associated with production of IgE antibodies and allergy) to a Th1 response (which is protective against allergic reactions), an effective dose of an immunostimulatory nucleic acid (or a vector containing a nucleic acid) alone or in conjunction with an allergen can be administered to a subject to *treat* or prevent an allergy.” Col. 34, lines 18-26 (emphasis added).

This connection between Th1 shift and applicability to therapy in the allergy context is mirrored in Applicants’ specification. *See, for example*, page 49, lines 9-10 (“TH1 responses are to be of particular importance in the treatment of allergies and AIDS.”) in conjunction with page 4, lines 9-11 (“The invention also includes naked gene expression vectors for use in manipulating cellular immune responses toward the TH1 compartment”).

Both recitations aim for the same goal that is well recognized in the art: reduction of allergy-associated IgE antibodies, which mediate the unpleasant symptoms of allergy (such as histamine release, leading to runny eyes, itching, etc.). While Applicants’ recitation is more concise than that of claim 3 of Krieg ’646, both convey the same concept and objective via reduction of allergy-associated IgE production.

Claim 3 of the Krieg ’646 patent recites that the recipient of the treatment is a “subject”, which is defined in the specification as “a human or vertebrate animal. . .”. Col. 13, lines 27-29. Applicants’ claim 204 recites “vertebrate”.

“An immunostimulatory nucleic acid in a plasmid, said immunostimulatory nucleic acid comprising 5’CG3’ wherein C is unmethylated.” Claim 3 of the Krieg ’646 patent recites “an immunostimulatory nucleic acid, comprising: 5’X₁CGX₂3’ wherein the immunostimulatory nucleic acid includes at least 8 nucleotides and . . . wherein X₁ and X₂ are nucleotides. . .” A plasmid is an obvious polynucleotide species in view of a polynucleotide of at least 8 nucleotides in length, and vice versa. In a plasmid, the recitation of X₁, X₂, etc. is rendered superfluous, as the CG sequence would *de facto* always be flanked by other nucleotides. The recitation of at

least 8 nucleotides is also rendered superfluous, as a plasmid must have at least 8 nucleotides. Conversely, a plasmid anticipates a polynucleotide of at least 8 nucleotides in length.

“Antigen which stimulates production of allergy-associated IgE antibodies in the vertebrate.” Claim 3 of the Krieg ‘646 patent recites “allergen”. One skilled in the art would readily recognize that an allergen is an antigen which stimulates an allergic response, and that an allergy in turn is an inappropriate immune response to the offending antigen. The *Academic Press Dictionary of Science and Technology* (1992) provides a standard dictionary definition of allergen (“an *antigen* that is capable of inducing an allergic reaction”)(emphasis added) and an allergy (“an exaggerated physical response to some antigen. . . resulting when histamine or histamine-like substances are released from injured cells.”).

It is also well known in the art that a hallmark of an allergic response is production of allergy-associated IgE antibodies in the subject having the allergic reaction. *Academic Press Dictionary of Science and Technology* (1992) provides a standard dictionary definition of IgE antibodies (“a class of immunoglobulins that are generally elicited by an allergen and that bind to the surfaces of mast cells”). Krieg’s ‘646 specification states that allergies “are generally caused by IgE antibody generation”. Col. 34, lines 7-9. Thus “allergen” and “an antigen which stimulates production of allergy-associated IgE antibodies” are essentially the same recitations.

“Wherein said antigen is encoded in the plasmid.” Claim 3 of the Krieg ‘646 patent recites that an “allergen” is administered. Applicants’ claim recites an obvious variation of administering the offending antigen, namely, that the antigen is encoded in the plasmid. Conversely, administering an antigen *per se* is obvious in view of administering an antigen which is encoded in a plasmid (polynucleotide). In terms of the role of antigen in modulating an immune response in the context of administering a CG-containing immunostimulatory sequence, an antigen-encoding sequence presents to the organism an antigen upon transcription and translation. One of ordinary skill would recognize that the delivery of an antigen encoded by a plasmid is an obvious alternative with respect to delivery of antigen *per se*. In terms of result, both an “antigen” and an “antigen encoded in a plasmid” stimulate an antigen-specific immune

response. Applicants also point out that claims of the Krieg '646 patent use these terms interchangeably. *See* claim 4 of the Krieg '646 patent, which recites “a vaccine antigen or an antigen encoded in a DNA vaccine”. Other claims of the Krieg '646 patent use the term “antigen encoded in a DNA vaccine” as a species with respect to an “antigen”. *See* claim 10 (“wherein the antigen is encoded in a DNA vaccine”; dependent from claim 6, which recites “an antigen”); claim 16 (“wherein the antigen is encoded in a DNA vaccine”; dependent from claim 14, which recites “an antigen”); claim 20 (“wherein the antigen is encoded in a DNA vaccine”; dependent from claim 18, which recites “an antigen”); claim 24 (“wherein the antigen is encoded in a DNA vaccine”; dependent from claim 22, which recites “an antigen”).

The Krieg '646 patent specification equates the use of “antigen” and an “antigen encoded in a polynucleotide”. The specification refers to the “antigen encoded by the [DNA] vaccine” as determining the specificity of the immune response, which is the same function that an antigen *per se* would serve in compositions containing immunostimulatory polynucleotides. Col. 33, lines 39-40. The Krieg '646 patent specification also describes expression vectors in the context of the invention and states that the invention includes expression vectors such as plasmids and “such other forms of expression vectors which serve equivalent functions [expression of an antigen] and which become known in the art subsequently hereto.” Col. 13, lines 40-46. Original claim 18 (which is part of the specification) recites “[a]n improved method of vaccination in a subject, comprising administering to the subject a vaccine antigen or a nucleic acid encoding the vaccine antigen and a nucleic acid of claim 1.”

If viewed as a species, an “antigen encoded by the plasmid” (a polynucleotide) anticipates the genus “antigen”. Conversely, the species of “antigen encoded by the plasmid” (a polynucleotide) is an obvious species in view of the genus “antigen”. Antigens encoded in DNA vaccines were known in the art as an immunogenic form of an antigen of interest. *See, for example, Nat. Medicine* (1995) 1:583-7 (“Preclinical Efficacy of a Prototype DNA Vaccine: Enhanced Protection Against Antigenic Drift in Influenza Virus”) and *Ann. NY Acad. Sci.* (1995)

772:1-294 (“DNA Vaccines: A New Era in Vaccinology”). Thus, an “antigen encoded by a polynucleotide” and an “antigen” are obvious and/or anticipated in view of each other.